

Editorial

Making a medicine
out of MDMA

Ben Sessa and David Nutt

**Summary**

From its first use 3,4-methylenedioxymethamphetamine (MDMA) has been recognised as a drug with therapeutic potential. Research on its clinical utility stopped when it entered the recreational drug scene but has slowly resurrected in the past decade. Currently there is enough evidence for MDMA to be removed from its Schedule 1 status of 'no medical use' and moved into Schedule 2 (alongside other misused but useful

medicines such as heroin and amphetamine). Such a regulatory move would liberate its use as a medicine for patients experiencing severe mental illnesses such as treatment-resistant post-traumatic stress disorder.

Declaration of interest

None.

Ben Sessa (pictured) is a consultant psychiatrist in substance misuse working for 'AddAction' in Weston-Super-Mare, North Somerset, and a senior research fellow at Cardiff University Medical School. David Nutt is the Edmond J. Safra Professor of Neuropsychopharmacology at Imperial College London, and former President of the European College of Neuropsychopharmacology.

For those of us researching the development of 3,4-methylenedioxymethamphetamine (MDMA) therapy for patients with post-traumatic stress disorder (PTSD) the drug's historical association with recreational ecstasy is a hindrance. Although clinical use precedes recreational ecstasy the media focuses primarily on the rare incidences of harm associated with misuses of the latter. After a quarter of a century of epidemiological evidence of MDMA's low rates of morbidity and mortality (even when used recreationally as ecstasy), as well as mounting data supporting clinical MDMA as a therapeutic agent, we feel it is time to concentrate on the objective evidence-based research. Otherwise, we risk denying a population of needy patients a potentially important treatment. An important step towards recognising MDMA as a medicine is to move it from Schedule 1 to Schedule 2 of the UK's drug classification system.

A brief history of MDMA in medicine

First synthesised in 1912 by the German pharmaceutical company Merck as a chemical precursor, MDMA failed to make an impact on the 1960s drug scene. In the 1970s a few psychotherapists were using it legally as a tool in couples therapy, where it was seen to help traumatised clients address repressed emotional memories without being overwhelmed by the negative affect that usually accompanies such memories. It was then banned in the mid-1980s in the wake of growing recreational use. No placebo-controlled studies were conducted with MDMA in the 1980s, but case-control studies showed MDMA could be used without adverse effects to produce qualitative improvements in psychological functioning and resolution of relationship difficulties.¹

Controlled clinical trials

A recent placebo-controlled study of participants with treatment-resistant PTSD showed that 85% of those in the MDMA group (compared with 15% in the placebo group) no longer had a

diagnosis of PTSD after three sessions of MDMA-assisted psychotherapy.² These results were sustained at 3.5 years long-term follow-up, with no further MDMA interventions required and many patients reducing or stopping their regular psychiatric medications.³ A subsequent Swiss MDMA study demonstrated substantial improvements for treatment-resistant PTSD.⁴

**How MDMA may work as an adjunct
to psychotherapy**

MDMA exerts its effects through 5-hydroxytryptamine (5-HT)_{1A}, 5-HT_{1B}, 5-HT_{2A}, dopamine and alpha-2 receptors. It also produces oxytocin release, which improves bonding and raises levels of empathy. Its multiple and varied effects make the drug a good candidate for facilitating psychotherapy – especially for patients with post-traumatic symptoms, in which helping the patient to reach a position of empathic understanding and compassionate regard is part of their resolution and remittance of symptoms.⁵

Participants given MDMA are more likely to use words relating to friendship, support and intimacy, in comparison to the drug methamphetamine, which by contrast reduced participants' discussions about compassion.⁶ MDMA appears to enhance the quality of social interactions and thereby improve relationships, recently tested using a simulated experimental paradigm of social exclusion by Frye *et al*, showing how participants taking MDMA exhibited reduced social exclusion phenomena.⁷ Similarly, MDMA enhances levels of shared empathy and prosocial behaviour compared with placebo.⁸ Furthermore, Wardle *et al* showed how MDMA can facilitate a faster detection of happy faces, and reduces the detection of negative facial expressions, which leads participants to view their social interaction partner as more caring.⁹ A recent study by Kirkpatrick *et al* comparing MDMA against intranasal oxytocin demonstrated the former produced greater improvements in prosocial communication.¹⁰ And the positive effects of MDMA appear consistent across different environments, with participants examined in San Francisco, Chicago and Basel demonstrating broadly similar prosocial outcomes.¹¹

Recently, several groups have used neuroimaging to explore the actions of MDMA in the brain. For example, Carhart-Harris *et al*, using magnetic resonance imaging blood oxygen level-dependent and arterial spin labelling techniques, showed that MDMA reduced amygdala and hippocampus activity and selectively attenuated the magnitude of negative memories.¹²

Current restrictions around the use of MDMA in the UK

Given the evidence that MDMA is a useful and safe adjunct to the treatment of PTSD and has plausible mechanisms of action, one might well ask why MDMA is not available for clinical use. The answer is simple – when MDMA was banned in the 1980s it was put into Schedule 1 of the 1971 UN convention and in the UK placed in Schedule 1 of the Misuse of Drugs Regulations 2001. Both regulatory systems define Schedule 1 drugs as those with ‘very limited medical use’. This is no longer defensible. So what does being in Schedule 1 mean for researchers and doctors who wish to prescribe it? In most countries Schedule 1 drugs are subject to stringent controls. In the UK one needs a special license to hold or use a Schedule 1 drug, whereas Schedule 2 drugs, such as heroin and morphine, much more addictive and dangerous than MDMA, are available in all hospitals. Schedule 1 licenses cost about £5000, can take a year to obtain and require special criminal record checks, extra-secure pharmacy safes and police inspections. Only four hospitals in the country presently have them. Furthermore, production sites and distributors need the special license too, which massively escalates costs and limits the number of companies able to manufacture and supply clinical-grade material.

Safety and risks

One must distinguish the clinical use of pure MDMA from the recreational use of ecstasy. The former involves moderate, infrequent medically supervised doses whereas the latter often involves high and frequent use, the risk of adulterants and the concomitant use of other drugs – especially cannabis, amphetamine and cocaine. There is no evidence that pure MDMA as proposed for therapy causes any lasting physiological or psychological harm.¹³ None of the controlled studies of MDMA-assisted therapy has demonstrated any significant neurophysiological impairments or evidence of dependence following its use clinically, validating the observed low risk of addiction when used recreationally. The fears about lasting neurophysiological damage, popularised in the 1990s, have since been challenged, further validating the epidemiological evidence of low rates of clinical problems associated with ecstasy use, despite its widespread popularity.¹⁴

The concept of risk–benefit analysis is important when considering any medical interventions – pharmacological or otherwise. With dozens of individuals with post-combat treatment-resistant PTSD dying by suicide every day,¹⁵ the massive social, financial and clinical burden of untreated PTSD is a far greater risk to society than the low risks associated with using MDMA in the clinical setting.

The future for MDMA research

Further Phase II MDMA-assisted psychotherapy for PTSD studies are happening, after which Phase III studies are planned across the globe. A planned functional magnetic resonance imaging study at Cardiff University will explore MDMA’s mechanism in individuals with post-combat PTSD to add more physiological data to the ongoing therapeutic studies. And an ongoing study underway in the USA is exploring MDMA’s ability to boost empathy and for adults with anxiety associated with autism.¹⁶ But for MDMA to become a medicine it needs to be removed from Schedule 1 and put alongside other therapeutic (but also misused) stimulants such as amphetamine and methamphetamine in Schedule 2. If

the UK government advisory body on drugs, the Advisory Council on the Misuse of Drugs, recommends this to the Home Secretary, regulations can then be amended within weeks. It is important to note that the UK is not legally obliged to adopt the UN structure for scheduling drugs; and based on medical advice put heroin in Schedule 2 against the UN recommendation. Similarly, in another example the UN placed tetrahydrocannabinol in Schedule 1 in 1971, but in the UK it is available (in the form of the drug sativex) and placed in Schedule 4. Moreover there is no reason to suppose putting MDMA into Schedule 2 would have any impact on illicit use of ecstasy, just as pharmaceutical heroin in Schedule 2 is almost never diverted into criminal hands.

We call on the Advisory Council on the Misuse of Drugs to recommend MDMA become a Schedule 2 drug. This will allow medical research to explore the full potential of MDMA as a medicine for treatment-resistant PTSD and other possible brain disorders.

Conclusion

MDMA has been subjected to inappropriate, non-evidence-based, legislative restrictions. These have not effectively reduced the harm or burden of recreational ecstasy use on society but they have effectively held back research on clinical MDMA. We urge the regulatory authorities to consider whether a move from Schedule 1 to Schedule 2 might more accurately reflect MDMA’s relative harms and safety, while also facilitating greater research of the substance for possible therapeutic uses within psychiatry.

Ben Sessa, MBBS, MRCPsych, AddAction, Weston-Super-Mare, and Cardiff University; **David Nutt**, DM, FRCP, FRCPsych, FMedSci, Neuropsychopharmacology Unit, Division of Brain Sciences, Faculty of Medicine, Imperial College London, UK

Correspondence: Ben Sessa, AddAction, 35 The Boulevard, Weston-Super-Mare, Somerset BS23 1PE, UK. Email: bensessa@gmail.com

First received 13 Jun 2014, accepted 7 Oct 2014

Acknowledgements

Thank you to Ilsa Jerome, Rudi Law and Les King for advice on this editorial.

References

- Greer G, Tolbert R. Subjective reports of the effects of MDMA in a clinical setting. *J Psychoactive Drugs* 1986; **18**: 319–27.
- Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol* 2010; **25**: 439–52.
- Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Martin SF, Yazar-Klosinski B, et al. Durability of improvement in PTSD symptoms and absence of harmful effects or drug dependency after MDMA-assisted psychotherapy: a prospective long-term follow-up study. *J Psychopharmacol* 2013; **27**: 28–39.
- Chabrol H. MDMA assisted psychotherapy found to have a large effect for chronic post-traumatic stress disorder. *J Psychopharmacol* 2013; **27**: 865–6.
- Sessa B. Could MDMA be useful in the treatment of PTSD? *Prog Neurol Psychiatry* 2012; **15**: 4–7.
- Bedi G, Cecchi GA, Slezak DF, Carrillo F, Sigman M, de Wit H. A window into the intoxicated mind? Speech as an index of psychoactive drug effects. *Neuropsychopharmacology* 2014; **39**: 2340–8.
- Frye CG, Wardle MC, Norman GJ, de Wit H. MDMA decreases the effects of simulated social rejection. *Pharmacol Biochem Behav* 2014; **117**: 1–6.
- Hysek CM, Schmid Y, Simmler LD, Domes G, Heinrichs M, Eisenegger C, et al. MDMA enhances emotional empathy and prosocial behavior. *Soc Cogn Affect Neurosci* 2013; Oct 23 (Epub ahead of print).

- 9 Wardle MC, de Wit H. MDMA alters emotional processing and facilitates positive social interaction. *Psychopharmacology (Berl)* 2014; **231**: 4219–29.
- 10 Kirkpatrick MG, Lee R, Wardle MC, Jacob S, de Wit H. Effects of MDMA and intranasal oxytocin on social and emotional processing. *Neuropsychopharmacology* 2014; **39**: 1654–63.
- 11 Kirkpatrick MG, Baggott MJ, Mendelson JE, Galloway GP, Liechti ME, Hysek CM, et al. MDMA effects consistent across laboratories. *Psychopharmacology (Berl)* 2014; **231**: 3899–905.
- 12 Carhart-Harris RL, Erritzoe D, Williams LTJ, Erritzoe D, Wall MB, Ferguson B, et al. The effects of acutely administered 3,4-methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers measured with arterial spin labeling and blood oxygen level-dependent resting state functional connectivity. *Biol Psychiatry* 2014; 10 Jan (Epub ahead of print).
- 13 Doblin R, Greer G, Holland J, Jerome L, Mithoefer MC, Sessa B. A reconsideration and response to Parrott AC (2013) “Human psychobiology of MDMA or ‘Ecstasy’: an overview of 25 years of empirical research”. *Hum Psychopharmacol* 2014; **29**: 105–8.
- 14 Selvaraj S, Hoshi R, Bhagwagar Z, Murthy NV, Hinz R, Cowen P, et al. Brain serotonin transporter binding in former users of MDMA (‘ecstasy’). *Br J Psychiatry* 2009; **194**: 355–9.
- 15 Kemp J, Bossarte R. *Suicide Data Report 2012*. US Department of Veterans Affairs, 2013 (<http://www.va.gov/opa/docs/Suicide-Data-Report-2012-final.pdf>).
- 16 Multidisciplinary Association for Psychedelic Studies (MAPS). *Protocol MAA-1: A Placebo-Controlled, Randomized, Blinded, Dose Finding Phase 2 Pilot Safety Study of MDMA Assisted Therapy for Social Anxiety in Autistic Adults*. Multidisciplinary Association for Psychedelic Studies (MAPS), 2013 (http://www.maps.org/research/mdma/MAA1_FINAL_Protocol_22Feb13_redact.pdf).

fallen stars

Léon Bonvin

Raymond Cavanaugh Jr

Born in the outskirts of Paris in 1834, Léon Bonvin was the son of a policeman and a seamstress. There were numerous siblings from multiple marriages, and money was scarce. Léon’s strongest bond was with his older brother François. They shared a desire to draw and a precocious aesthetic sensibility. Apprenticed to a printer in his adolescence, François would give the younger Léon artistic advice for the remainder of his life.

Most of Léon’s earliest works were charcoal renditions of his austere surroundings. He would later work in graphite, pen and ink, and eventually in the watercolour medium, with which he would carve his niche. Oil painting was a rare activity for him, because he was rarely able to afford oil paints.

Though lacking in materials, Bonvin benefited from his elder brother’s guidance. François suggested that he study the Dutch masters and pay particular attention to their ‘meticulous realism and use of outline’. In time, the younger brother would employ sepia-toned ink outlines to produce his own ‘meticulous realism’ in the form of watercolours with startling, quasi-photographic effects.

However, this stylistic innovation did little to enhance Bonvin’s overall quality of life. Forced to work tirelessly at his job as innkeeper, there was precious little time for the artistic vocation. Early morning and sunset were usually the only times at which he could practise his coloured magic.

The online art publication *The Blue Lantern* explores the psychodynamic elements of Bonvin’s *Interior of a House with an Open Door*. This painting has a very claustrophobic feel, which likely reflects its painter’s ongoing sentiments of ‘frustration’ and ‘confinement’. Though the painting, through its ‘open door’, includes a ‘glimpse of a wider world’, this glimpse is ‘obscured by blazing sunlight’.

The early 1860s saw Bonvin marry, start a family, and sink further into poverty. By January 1866 his financial situation had become dire. Carrying as many paintings as he could, he headed to Paris and approached an art dealer. ‘Too dark’, was the dealer’s response. Having been dismissed with these few words, the starving artist was sent on his way, not one franc the richer. Emotionally drained, Bonvin went to a hill that overlooked the plains of Issy. This view had inspired some of his most passionately painted watercolours.

Here, hours later, the painter was found hanging from a tree. If there was any good to come of this demise, it was that a posthumous charity auction of his works raised enough money to spare his family from utter destitution.



Léon Bonvin (French, 1834–1866) *Landscape with a Bare Tree and a Plowman*, 1864. Pen and brown ink, watercolour, and gum Arabic, 18.1 × 16.2 cm. The J. Paul Getty Museum, Los Angeles. Digital image courtesy of the Getty’s Open Content Program.